Advanced Regression: 1b Linear and generalised linear models (Part I)

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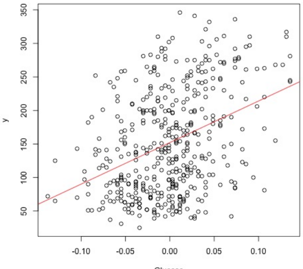
Main aim

Regression models are used to investigate association between

- an outcome variable y
- potential explanatory variables (or predictors) $x = (x_1, x_2, \ldots, x_p)$

The statistical idea is to see if the $x_1, x_2, \ldots, x_p$ can give an adequate description of the variability of the outcome y.



Motivations

1. **Understand** how the predictors affect the outcome.
   - Example: We conduct an observational study focusing on type 2 diabetes as outcome. Our aim is to understand which risk factors are associated with the risk of type 2 diabetes.
2. **Predict** the outcome of new observations, where only the predictors are observed, but not the outcome.
   - Example: We study type 2 diabetes and want to predict disease progression. Our aim is to identify individuals with poor prognosis and improve their treatment.

The linear model

$$y = \alpha + x\beta + \epsilon$$

- y: Outcome, response, dependent variable
  Dimension: $n \times 1$
- x: Regressors, exposures, covariates, input, explanatory, or independent variables
  Dimension: $n \times p$
- ϵ: Residuals, error
- α: Intercept
- β: Regression coefficients

Parameters to estimate:

- α: intercept
  Baseline level, the expected mean value of y when all $x = 0$
- $\beta = (\beta_1, ..., \beta_p)$: vector of regression coefficients
- β_j: regression coefficients of variable x_j
  The expected change in y for a one-unit change in x_j when the other covariates are held constant.

Observed data:

- y: Outcome or response
- x: Regressors, exposures, covariates, input, explanatory or independent variables
  - ◇ $i = 1, ..., n$ samples
  - ◇ $j = 1, ..., p$ variables

Estimates: Ordinary least squares (OLS)

$$\hat{\beta}_{OLS} = \underbrace{(x^t x)^{(-1)}}_{p \times p} \underbrace{x^t}_{p \times n} \underbrace{y}_{n \times 1}$$

- Inversion of $\underbrace{(x^t x)^{(-1)}}_{p \times p}$ requires $x^t x$ to be of full rank (Lecture 2b).
- Alternative representation:

$$\hat{\beta} = \frac{\hat{cov}(x, y)}{\hat{cov}(x)}$$

where the sample covariance is defined as:

  - $\hat{cov}(x, y) = \frac{1}{n} \sum_{i=1}^{n} (x_i - \bar{x})(y_i - \bar{y})$
  - $\hat{cov}(x) = \frac{1}{n} \sum_{i=1}^{n} (x_i - \bar{x})(x_i - \bar{x})$

Example: Diabetes data

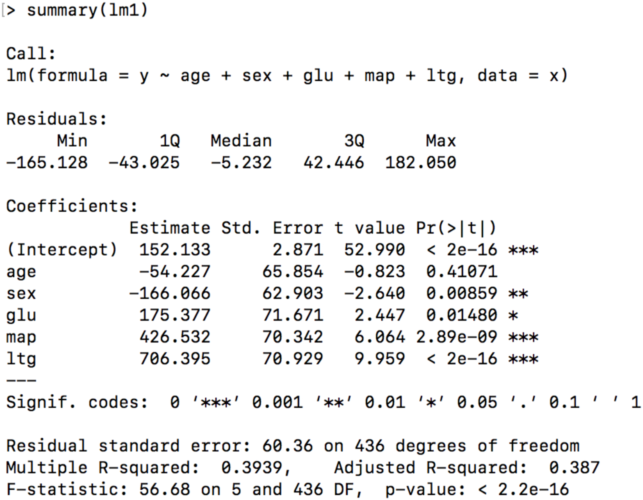
- y: quantitative measure of disease progression one year after baseline (vector)
- x: predictor matrix
  - clinical parameters: age, sex, bmi
  - map: blood pressure
  - tc: total cholesterol
  - ldl: low-density lipoprotein
  - hdl: high-density lipoprotein
  - tch: total cholesterol over hdl
  - ltg: triglycerides
  - glu: glucose
- $n = 442$: sample size

The `lm()` command in R

- `lm(y ~ age+sex+glu+map+ltg, data = x)`
- Formula `y ~ x1+x2+x3`
  - left of ∼: outcome
  - right of ∼: predictors
- It is also possible to enter a full matrix x (transform by `as.matrix`) as multivariable set of predictors: `y ~ x`
- An intercept is always included, to turn off add `-1`

Interpreting the summary.lm() command

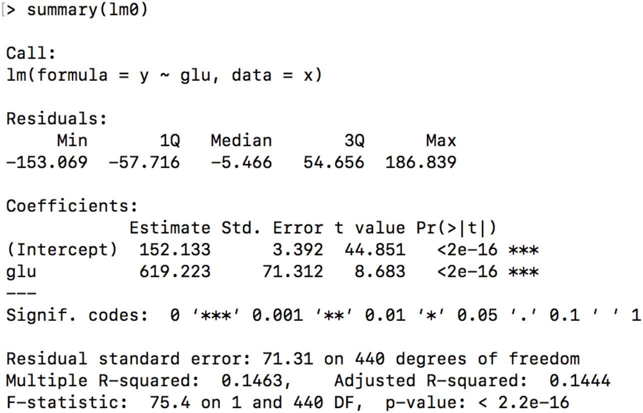
- `summary.lm(lm(y ∼ age+sex+glu+map+ltg, data = x))`



```
> summary(lm1)

Call:
lm(formula = y ~ age + sex + glu + map + ltg, data = x)

Residuals:
     Min       1Q   Median       3Q      Max 
-165.128  -43.025   -5.232   42.446  182.050 

Coefficients:
            Estimate Std. Error t value Pr(>|t|)    
(Intercept)  152.133      2.871  52.990  < 2e-16 ***
age          -54.227     65.854  -0.823  0.41071    
sex         -166.066     62.903  -2.640  0.00859 ** 
glu          175.377     71.671   2.447  0.01480 *  
map          426.532     70.342   6.064 2.89e-09 ***
ltg          706.395     70.929   9.959  < 2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 60.36 on 436 degrees of freedom
Multiple R-squared:  0.3939,	Adjusted R-squared:  0.387 
F-statistic: 56.68 on 5 and 436 DF,  p-value: < 2.2e-16
```

Difference between univariable and multivariable regression

- summary.lm(lm(y ~glu))



```
> summary(lm0)

Call:
lm(formula = y ~ glu, data = x)

Residuals:
     Min       1Q   Median       3Q      Max 
-153.069  -57.716   -5.466   54.656  186.839 

Coefficients:
            Estimate Std. Error t value Pr(>|t|)    
(Intercept)  152.133      3.392  44.851   <2e-16 ***
glu          619.223     71.312   8.683   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 71.31 on 440 degrees of freedom
Multiple R-squared:  0.1463,	Adjusted R-squared:  0.1444 
F-statistic:  75.4 on 1 and 440 DF,  p-value: < 2.2e-16
```

- Reduction of the regression coefficient from 619 to 175 after conditioning on other covariates. → attenuation of the effect.

Further estimates

- Weighted least squares

$$\hat{\beta}_{WLS} = \underbrace{(x^t wx)^{(-1)}}_{p \times p} \underbrace{x^t}_{p \times n} \underbrace{w}_{n \times n} \underbrace{y}_{n \times 1}$$

  where w is a $n \times n$ diagonal weight matrix

- Maximum likelihood
- Bayesian linear regression (Module: Bayesian Statistics)

Fitted values and residuals

- Fitted values

$$\hat{y} = x\hat{\beta} = \underbrace{x(x^t x)^{-1} x^t}_{h} y$$

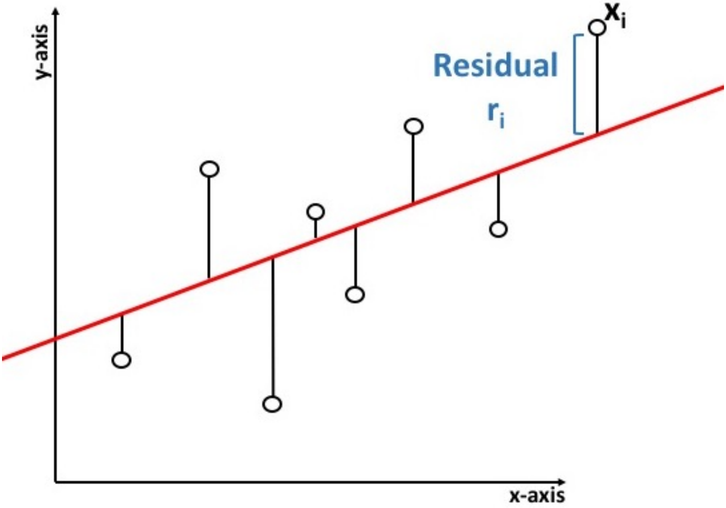
- Hat matrix h
- Residuals are the difference between the fitted values (predicted by the model) and the actual observed outcome.

$$r_i = \hat{y}_i - y_i$$

- The residuals are a vector $r = (r_1, ..., r_n)$ of length n.

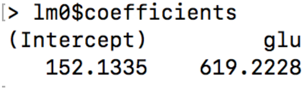
Residuals are an important quantity for model diagnostics.

Fitted values and residuals



lm(): Fitted values and residuals

- First fit a linear model and save it in the object lm0
  `lm0 = lm(y∼x)`
- The linear model object lm0 contains
  - Regression coefficients: `lm0$coefficients`



```
> lm0$coefficients
(Intercept)         glu
   152.1335    619.2228
```

  - Fitted values: `lm0$fitted.values`
  - Residuals: `lm0$residuals`

Assumptions

I. Linearity: There is a linear relationship between x and y

II. Weak exogeneity: The predictors x are viewed as fixed variables; there is no measurement error on x.

III. Constant variance (homoscedasticity): All residuals have the same variance.

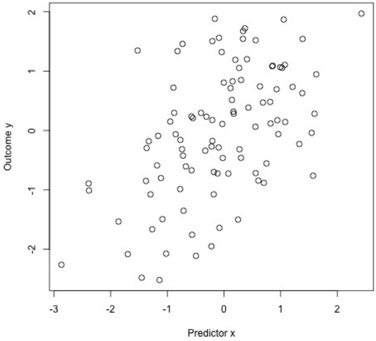
IV. No perfect multicollinearity: No predictor can be expressed as a linear combination of the other predictors (Lecture 2b).

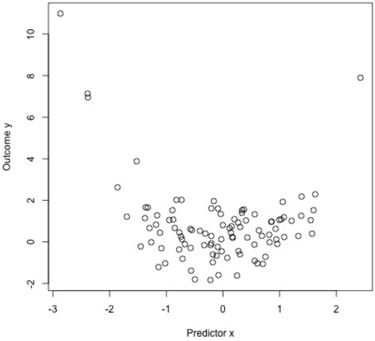
V. Independent errors: The residuals are uncorrelated (e.g. in time-series the error of time point t will depend on the error of time point $t-1$) and independent of x.

Further assumptions

- Normal-distributed errors:
  The residuals are normal-distributed.
  Note: This is not required for the OLS estimate, but for the Maximum Likelihood estimation.
- Outlier: observation point that is distant from other observations.
  It is recommended to check the data for outliers, which can arise because of many reasons:
  - Measurement error (remove)
  - Errors in the pre-processing steps (fix or remove)
  - 'True' biological outliers (follow-up)
- Influential variants: Cook's distance

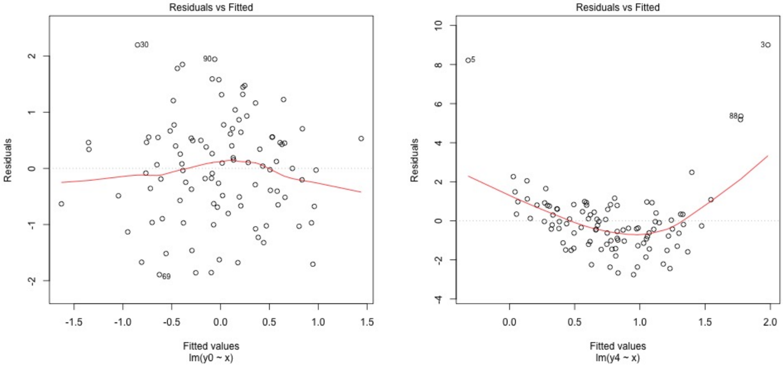
Diagnostic plots: Linear relationship





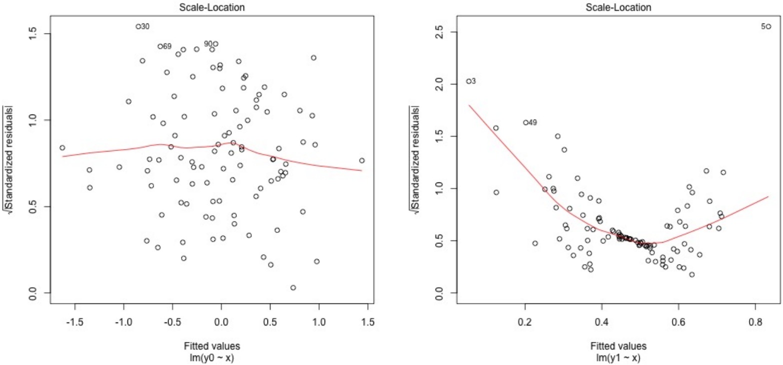
- Scatterplot of y against x

Diagnostic plots: Linear relationship



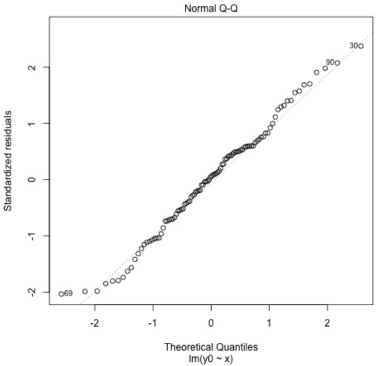
- Scatterplot of residuals (y-axis) against fitted values (x-axis)

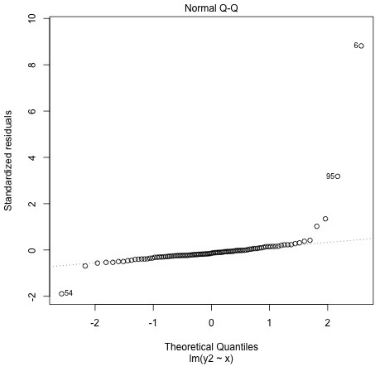
Diagnostic plots: Homoscedasticity



- Scatterplot of standardised residuals (y-axis) against fitted values (x-axis)

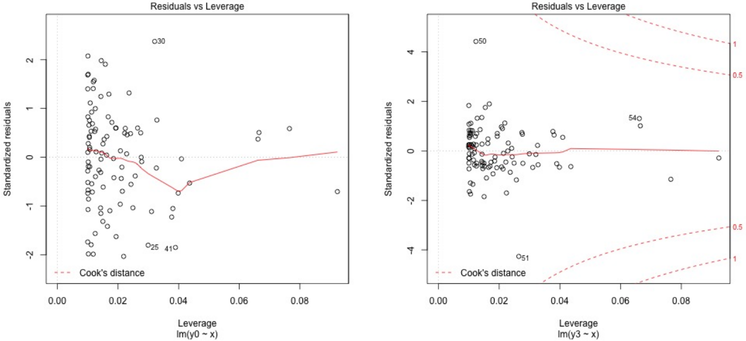
Diagnostic plots: Normal-distribution of residuals





- Q-Q plots of observed residuals (y-axis) against theoretical values under the Normal distribution (x-axis)

Diagnostic plots: Outliers



- Scatterplot of standardised residuals (*y*-axis) against Cook's distance (*x*-axis)
- Cook's distance measures the effect of deleting a given observation (sum of all the changes in the regression model when observation *i* is removed)

lm(): Diagnostics

- Linear relationship and outliers (Scatterplot of y against x)
  ```
  plot(x,y)
  abline(lm0, col='red')
  ```
- Linear relationship and outliers (Residuals against fitted values)
  ```
  plot(lm0, which=1)
  ```
- Homoscedasticity (Standardised residuals against fitted values)
  ```
  plot(lm0, which=3)
  ```
- Normal-distribution of residuals (Q-Q plots of observed residuals against theoretical values under the Normal distribution)
  ```
  plot(lm0, which=2)
  ```
- Influential variants: (Standardised residuals against Cook's distance)
  ```
  plot(lm0, which=5)
  ```

Prediction using linear models

1. Assume we have a database with n type 2 diabetes cases, where we have measured the following data:
   - y: quantitative measure of disease progression one year after baseline (vector)
   - x: predictor matrix including clinical data (age, sex, bmi), blood pressure and triglycerides

   This is our training data $y_$train and $x_$train.
2. For a new case we only have the predictor matrix x_{new}, but not y_{new}.
3. Goal: For each new type 2 diabetes case we want to predict y_{new}, his/her progression one year later.

lm(): Predictions

1. Use the linear model to learn a prediction rule from the training data, where both x and y are observed on the same individuals.

   ```
   lm_train =
   lm(formula=y_train∼age+sex+bmi+map+ltg,
   data=x_train)
   ```

2. Predict the outcome based on the prediction rule and the predictors of the new data.

   ```
   predict.lm(lm_train,x_new)
   ```

Take away: Linear models

- Motivation why to use linear models
  (To understand and to predict)
- Model fit using ordinary least squares
- Interpretation of the regression coefficients
- Residuals and fitted values
- Model diagnostics
- Using the linear model to predict